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EXAMINER

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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 10/560,836
Filing Date: March 30, 2006
Appellant(s): GUGLIELMOTTI ET AL.

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 5/12/2008 appealing from the Office action mailed 9/12/2007.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6,326,385	Wickenden	12-2001
20040038874	Omoigui	8-2002

Gaster et al (EP 0630736)

Smith et al. (Neuroscience Letters, 271, 1999, 61-64)

Jorum et al. (Pain, 101, 2003, 229-235)

Burstein et al. (Brain, 2000, 123, 1703-1709)

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 6-12, 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gaster et al (EP 0630736) in view of Smith et al. (Neuroscience Letters, 271, 1999, 61-64) and further in view of Jorum et al. (Pain, 101, 2003, 229-235).

Gaster et al. teaches the compounds of formula I (claim 1) to be 5-HT₄ antagonists (p1 lines 6-8) and further teaches a method of treatment of irritable bowel syndrome, migraine etc in mammals (p6, lines 42-43) comprising administering these compounds.

The reference does not teach a method of treatment of neuropathic pain comprising administering such compounds.

Smith et al. teaches that 5-HT4 receptor antagonist such as SB 207266 potentiates inhibition of intestinal allodynia (see Abstract, p63, lines 11-12).

The reference does not teach allodynia to be neuropathic pain.

Jorum et al. teaches that allodynia and hyperalgesia are frequent clinical findings in patients with neuropathic pain (p 229, lines 1-5).

It would have been obvious to one skilled in the art to use the compounds of formula I in the treatment of neuropathic pain. The motivation to do is provided by Gaster, Smith et al. and Jorum et al. Gaster et al. teaches the compounds of formula I (claim 1) to be 5-HT4 antagonists. Smith et al. teaches that 5-HT4 receptor antagonist such as SB 207266 shows an anti-allodynic activity and Jorum et al. teaches that allodynia and hyperalgesia are frequent clinical findings in patients with neuropathic pain. Hence inhibiting allodynia in patients provides a method of treatment of neuropathic pain. One of ordinary skill in the art would have been motivated to use one 5-HT4 receptor antagonist (compound of formula I) for another 5-HT4 receptor antagonist (SB 207266) in the treatment of allodynia (clinical finding of neuropathic pain) in expectation of success as Smith teaches an anti-allodynic effect of an 5-HT4 receptor antagonist.

Claims 6-12, 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gaster et al (EP 0630376) in view of Burstein et al. (Brain, 2000, 123, 1703-1709) and further in view of Jorum et al. (Pain, 101, 2003, 229-235).

Gaster et al's teachings as above.

The reference does not teach a method of treatment of neuropathic pain comprising administering such compounds.

Burstein et al. teaches that most migraine patients exhibit cutaneous allodynia during a fully developed migraine attack (See Abstract).

The reference does not teach allodynia to be neuropathic pain.

Jorum et al. teaches that allodynia and hyperalgesia are frequent clinical findings in patients with neuropathic pain (p 229, lines 1-5).

It would have been obvious to one skilled in the art to use the compounds of formula I in the treatment of neuropathic pain. The motivation to do is provided by Gaster et al, Burstein et al. and Jorum et al. Gaster et al teaches the administration of a 5-HT₄ antagonist is of potential benefit in relieving migraine attack. Burstein et al. teaches that cutaneous allodynia is exhibited during a fully developed migraine attack and Jorum et al. teaches that allodynia and hyperalgesia are frequent clinical findings in patients with neuropathic pain. Hence by treating migraine attacks in patients allodynia is treated and in turn the neuropathic pain.

Claims 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gaster et al (EP 0630376) in view of Smith et al. (Neuroscience Letters, 271, 1999, 61-64) and further in view of Jorum et al. (Pain, 101, 2003, 229-235) as applied to claims 6-12, 14-17 and further in view of Wickenden et al. (U.S. 6,326,385).

Gaster et al., Smith et al. and Jorum et al's teachings discussed as above.

The references do not teach the subject has neuropathic pain associated with disorders such as diabetes, cancer, trigeminal neuralgia etc.

Wickenden et al. teach that neuropathic pain is associated with injury to the central or peripheral nervous system due to cancer, diabetes, diabetic neuropathy, trigeminal neuralgia (col. 27, claim 8).

It would have been obvious to one skilled in the art to use the compounds of formula I in the treatment of neuropathic pain associated with diabetes, cancer or trigeminal neuralgia. The motivation to do is provided by Gaster, Smith et al. and Jorum et al. Gaster teaches the compounds of formula I as 5-HT₄ receptor antagonists. Smith et al. teaches that 5-HT₄ receptor antagonist such as SB 207266 shows an anti-allodynic activity and Jorum et al. teaches that allodynia and hyperalgesia are frequent clinical findings in patients with neuropathic pain. One of ordinary skill in the art would have been motivated to use one 5-HT₄ receptor antagonist (compound of formula I) for another 5-HT₄ receptor antagonist (SB 207266) in the treatment of allodynia (clinical finding of neuropathic pain) in expectation of success as Smith teaches an anti-allodynic effect of an 5-HT₄ receptor antagonist. One of ordinary skill in the art would have been motivated by expectation of success in using compounds of formula I of the instant application in the treatment of neuropathic pain associated with disorders such as diabetes, cancer or trigeminal neuralgia.

Claims 20-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gaster et al (EP 0630736) in view of Smith et al. (Neuroscience Letters, 271, 1999, 61-64) and further in view of Jorum et al. (Pain, 101, 2003, 229-235) as applied to claims 6-12, 14-17 and further in view of Omoigui (US 2004/0038874, effective filing date Aug 22 2002).

Gaster et al., Smith et al. and Jorum et al's teachings discussed as above.

The references do not teach the subject has neuropathic pain associated with disorders such as trigeminal neuralgia, trauma, post-herpetic syndrome etc. and the route of administration of compound of formula I.

Omoigui teach a method of treating persistent pain disorders including neuropathic pain by inhibiting the biochemical mediators of inflammation in a subject comprising administering to said subject a therapeutically effective dosage of said inhibitor such as serotonin receptor antagonist (see Abstract, p 11, claim 1, p 13, claim 80). The reference further teaches the underlying basis for pain including neuropathic is inflammation and antagonism of inflammatory response will relieve pain of every type, origin and character (p 1, para 004). The reference teaches that hallmarks of neuropathic pain are chronic allodynia and hyperalgesia (para 0072). The reference teaches persistent pain disorder is neuropathic pain syndrome including neuralgia, post herpetic neuralgia (p 11, claim 12, 36). The reference further teaches that serotonin receptor antagonist is administered intramuscularly, intravenously, subcutaneously, orally or rectally.

It would have been obvious to one skilled in the art to use the compounds of formula I in the treatment of neuropathic pain associated with neuralgia, trigeminal neuralgia or post herpetic syndrome. The motivation to do is provided by Gaster, Smith et al and Omoigui. Gaster teaches the compounds of formula I as 5-HT₄ receptor antagonists. Smith et al. teaches that 5-HT₄ receptor antagonist such as SB 207266 shows an anti-allodynic activity. Omoigui teach a method of administering to said

Art Unit: 1616

subject a therapeutically effective dosage of inhibitor such as serotonin receptor antagonist for the treatment of neuropathic pain such as trigeminal neuralgia, post herpetic syndrome etc. In addition, Omoigui further teach hallmarks of neuropathic pain are chronic allodynia and hyperalgesia. One of ordinary skill in the art would have been motivated to use one 5-HT₄ receptor antagonist (compound of formula I) for another 5-HT₄ receptor antagonist (SB 207266) in the treatment of allodynia (clinical finding of neuropathic pain) in expectation of success as Smith teaches an anti-allodynic effect of an 5-HT₄ receptor antagonist. One of ordinary skill in the art would have been motivated by expectation of success in using 5-HT₄ receptor antagonist in a method of treatment of neuralgia or post herpetic syndrome as Omoigui teaches serotonin receptor antagonists are effective in the treatment of neuropathic pain with such syndromes.

(10) Response to Argument

(1) Claims 6-12 and 14-17 under U.S.C 103(a) as being unpatentable over Gaster et al. EP 0630376, in view of Smith et al. Neurosci. Lett, 271;66 and Jorum et al. Pain, 101:229.

Applicants' argue that there is no suggestion in the prior art as a whole to administer a compound of formula I to treat neuropathic pain. In response, Gaster et al. teaches the compounds of formula I (claim 1) to be 5-HT₄ antagonists and further teaches a method of treatment of irritable bowel syndrome, migraine etc in mammals comprising administering these compounds. Smith et al. teach a method of

Art Unit: 1616

administering a 5-HT₄ antagonist (SB-202266) along with a 5-HT₃ antagonist (granisetron). The reference further teaches that 5-HT₄ receptor antagonist potentiates the inhibition of intestinal allodynia. The reference in conclusion (p 64, lines (20-22) teaches that the data suggests a fundamental influence of the 5-HT₄ receptor on 5-HT invoked intestinal allodynia. The instant invention is directed to a method of treating neuropathic pain comprising administering a compound that is a 5HT-4 antagonist. Smith et al. teach a method of inhibition of intestinal allodynia comprising administering a 5HT-4 antagonist. Jorum et el. has been cited to show that allodynia and hyperalgesia are frequent clinical findings in patients with neuropathic pain. Hence it would have been obvious to one of ordinary skill in the art at the time of the invention to administer a compound of the claimed invention a 5HT-4 antagonist in a method of treatment of allodynia from the studies of Smith. One having ordinary skill in the art would have been motivated in administering the compounds claimed, 5HT-4 antagonists in a method of treatment of neuropathic pain because of expectation of success as well in achieving therapeutic benefits of inhibiting allodynia and thus relieving neuropathic pain.

Applicants' argue that the prior art does not disclose or suggest that thermal allodynia such as that disclosed by Jorum can be treated with the class of 5-HT₄ antagonists and Smith does not say this and Jorum in fact uses a completely different class of drug. In response, Jorum et el. has been cited only to show that allodynia and hyperalgesia are frequent clinical findings in patients with neuropathic pain.

Applicants' argue that office has not explained why a compound of formula I would exhibit similar properties to the structurally distinct SB-207266 compound of

Art Unit: 1616

Smith. In response, Gaster et al. teaches the compounds of formula I (claim 1) to be 5-HT4 antagonists and Smith teach SB-207266 to be 5-HT4 antagonist. The instant invention is directed to a method of treating neuropathic pain comprising administering a compound that is a 5HT-4 antagonist. Smith et al. teach a method of inhibition of intestinal allodynia comprising administering a 5HT-4 antagonist. Jorum et el. has been cited to show that allodynia and hyperalgesia are frequent clinical findings in patients with neuropathic pain. Hence it would have been obvious to one of ordinary skill in the art at the time of the invention to administer a compound of the claimed invention a 5HT-4 antagonist in a method of treatment of allodynia from the studies of Smith.

Applicants' argue that Jorum does not remedy the deficiencies of Gaster or Smith. Jorum discloses that Alfentanil significantly reduced cold allodynia and it is a non-analogous art because it discloses a different class of drugs and does not disclose compounds of formula. In response, Jorum et al. has been used as a secondary reference to show allodynia and hyperalgesia are frequent clinical findings in patients with neuropathic pain and in no way as a reference to the drug Alfentanil.

(2) Claims 6-12 and 14-17 under U.S.C 103(a) as being unpatentable over Gaster et al. EP 0630376, in view of Burstein et al. Brain, 123:1703 and Jorum et al. Pain, 101:229.

Applicants' argue that there is no link whatsoever between migraine and neuropathic pain and thus there cannot be any reasonable expectation of success for treating neuropathic pain using a compound that treats allodynia or migraine not associated with nerve damage. In response, Gaster et al. teaches the compounds of

Art Unit: 1616

formula I (claim 1) to be 5-HT₄ antagonists and further teaches a method of treatment of migraine in mammals comprising administering these compounds. Burstein et al. teaches that most migraine patients exhibit cutaneous allodynia during a fully developed migraine attack. Also, the document submitted by Applicant Allodynia (Wikipedia, the free encyclopedia) teaches that Allodynia, a clinical feature of many pain conditions such as migraine, postherpetic neuralgia, fibromyalgia and neuropathies (Heading: Causes – lines 1-2). Applicants' claim (claim 20) that neuropathic pain is associated with post-herpetic syndrome. As stated earlier, Jorum teaches that allodynia and hyperalgesia are frequent clinical findings in patients with neuropathic pain. In addition other prior art such as Omoigui teaches that hallmarks of neuropathic pain are chronic allodynia and hyperalgesia. Hence it would have been obvious to one of ordinary skill in the art at the time of the invention that allodynia is a clinical feature of migraine and allodynia is a clinical feature of neuropathic pain. Thus it would have been obvious to one of ordinary skill in the art at the time of the invention that treating migraine would alleviate allodynia, (associated with migraine) a clinical feature of neuropathic pain. Thus migraine is linked to neuropathic pain via the clinical feature allodynia. Hence by treating migraine attacks in patients allodynia is treated and in turn the neuropathic pain. It would have been obvious to try the compounds of the instant invention that has been taught to be useful in treating migraine in a method of treatment of neuropathic pain because allodynia is a clinical feature of migraine and allodynia is hallmark of neuropathic pain. Hence there is a reasonable expectation of success as the compounds of the instant invention are known to be useful in treating migraine.

Applicants' argue that Burstein teaches or suggests that any class of drugs capable of treating cutaneous allodynia will successfully treat migraine or neuropathic pain. In response, the secondary reference has been used to show the development of cutaneous allodynia during a migraine attack in most migraine patients. Gaster et al teaches the administration of a 5-HT₄ antagonist is of potential benefit in relieving migraine attack. Hence it would have been obvious to one of ordinary skill in the art at the time of the invention that cutaneous allodynia is treated when migraine is treated. Hence by treating migraine attacks in patients, allodynia (a clinical symptom of neuropathic pain) is treated and in turn the neuropathic pain.

(3) Claims 18-20 are rejected under U.S.C. 103(a) as being unpatentable over Gaster et al. EP 0630376, in view of Smith et al. Neurosci. Lett, 271;66 and Jorum et al. Pain, 101:229 and further in view of Wickenden, U.S Patent 6,326,385.

Applicants' argue that Wickenden does not disclose a compound of formula I or provide a reasonable expectation of success for treatment of neuropathic pain with such a compound. In response, Wickenden has been cited to show that neuropathic pain is associated with injury to the central or peripheral nervous system due to cancer, diabetes, diabetic neuropathy, trigeminal neuralgia. As stated earlier, Gaster teaches the compounds of formula I and further teaches them as 5-HT₄ antagonist and the secondary reference associates allodynia with 5-HT₄ receptor antagonists and allodynia is a clinical feature of neuropathic pain.

Art Unit: 1616

(4) Claims 20-23 are rejected under U.S.C. 103(a) as being unpatentable over Gaster et al. EP 0630376, in view of Smith et al. Neurosci. Lett, 271;66 and Jorum et al. Pain, 101:229 and further in view of Omoigui et al. (US. 2004/0038874).

Applicants' argue that teachings of Omoigui are hypothetical, and the patent is based on a literature reference and a plain reading of Omoigui does not reveal a common mechanism linked to substance P between the naturopathic pain and pain associated with migraine and there is no reasonable expectation of success in the treatment of both migraine and neuropathic pain from Omoigui. In response, Omoigui has been cited to show that hallmarks of neuropathic pain are chronic allodynia and hyperalgesia and neuropathic pain syndrome including neuralgia, post herpetic neuralgia and serotonin receptor antagonist can be administered intramuscularly, intravenously, subcutaneously, orally or rectally.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

Art Unit: 1616

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Conferees:

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